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	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L8	('b7-1') same ('b7-2')same (antibod$) and (sle or lupus)	119	L8
	DB=USPT,PGPB; PLUR=YES; OP=ADJ		
L7	L6 and (sle or lupus)	22	L7
L6	b7$ same (antibod$) same (rapamycin)	35	L6
L5	L4 and (sle or lupus)	125	L5
L4	b7$ and rapamycin	185	L4
L3	L2 and b7$	1	L3
L2	collins-mark$	80	L2
L1	sypek-joseph$	1	L1

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Term	Documents
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B7-2S	0
SLE.DWPI,EPAB,JPAB,USPT,PGPB.	2223
SLES.DWPI,EPAB,JPAB,USPT,PGPB.	214
LUPUS.DWPI,EPAB,JPAB,USPT,PGPB.	13382
LUPU.DWPI,EPAB,JPAB,USPT,PGPB.	288
ANTIBOD$	0
ANTIBOD.DWPI,EPAB,JPAB,USPT,PGPB.	582
ANTIBODAY.DWPI,EPAB,JPAB,USPT,PGPB.	1
(('B7-1') SAME ('B7-2')SAME (ANTIBOD$) AND (SLE OR LUPUS)).USPT,PGPB,JPAB,EPAB,DWPI.	119

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L7: Entry 5 of 22 File: PGPB Oct 17, 2002

DOCUMENT-IDENTIFIER: US 20020150580 A1
TITLE: Recombinant antibodies for human therapy

Detail Description Paragraph (11):
[0053] In a particularly preferred embodiment, the invention provides a specific recombinant referred to as CE9.1 (see Example 3) primate/human chimeric monoclonal antibody which is directed against the human CD4 antigen. This recombinant antibody has particular utility as an immunosuppressant and is especially useful for the treatment of autoimmune diseases such as rheumatoid arthritis. As described in greater detail in the Examples, in particular Example 3, this recombinant antibody is generated by grafting the antigen binding variable Fv domains from cynomolgus macaque to human constant IgG.sub.1 and gamma domains. More particularly, this antibody contains a human gamma 1 domain. The resultant recombinant antibody sequences are indistinguishable from human immunoglobulin sequences. As a result, this antibody upon in vivo administration in humans should exhibit reduced immunogenicity and longer serum half-life compared to similar murine monoclonal or mouse-human chimeric antibodies directed to CD4. This antibody binds to domain 1 of human, but not macaque, CD4, a region which is involved in the interaction with MHC Class II molecules on antigen presenting cells. Potent immunomodulatory activity has been observed with this antibody both in vitro and in vivo. Given these properties, i.e., reduced immunogenicity, longer half-life and potent immunosuppression, indicate that this antibody should be particularly suitable for long term therapy of diseases where immunosuppression is desirable, e.g., autoimmune disorders and chronic inflammatory diseases such as rheumatoid arthritis. However, it is expected that this antibody should be useful for the treatment of many other disease conditions including, by way of example, Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type I-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, multiple sclerosis, male infertility, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, inflammatory bowel disease syndrome, Sjogren's syndrome, psoriasis, rheumatoid arthritis, dermatomyositis, scleroderma, mixed tissue connective disease, discoid lupus erythematosus, systemic vasculitis, and systemic lupus erythematosus (SLE). In the preferred embodiment, however, the disease indication will comprise rheumatoid arthritis.

Detail Description Paragraph (13):
[0055] Essentially, the subject recombinant anti-CD4 monoclonal antibody or other antibodies produced according to the invention should mediate therapeutic activity by arresting or altering the destructive activity of CD4.sup.+ cells, particularly during acute phases of autoimmune disorders such as rheumatoid arthritis. Thus, administration of antibodies according to the invention will result in a state of immunological unresponsiveness (anergy) or long term tolerance to the insulting antigens (or specific tissues) that sustain the underlying disease without compromising normal host defenses against opportunistic infections. Apart from RA, CD4 monoclonal antibodies should be beneficial in the treatment of the above-identified diseases and afford particular application for the treatment of insulin-dependent diabetes mellitus, systemic lupus erythematosus, cirrhosis, inflammatory bowel disease, multiple sclerosis, as well as other autoimmune diseases.

Detail Description Paragraph (25):
[0067] The subject CE9.1 antibody has also been tested in humans. For example, the activity of the subject CE9.1 antibody has also been evaluated in single dose-escalating phase 1 trials in rheumatoid arthritis patients. These results were very promising. Specifically, about half of the patients who were administered exhibited at least a 30% improvement in their tender joint scores, with the adverse event profile being extremely benign. Moreover, as discussed supra, while it was initially assumed that CE9.1 would be depleting, in fact this antibody exhibited only partial and transient depletion upon single administration. The partial non-depleting nature of this antibody may be beneficial because in a number of animal studies it has been reported that CD4.sup.+ T cell depletion is apparently not necessary for efficacy of CD4 monoclonal antibodies. (See Carteron et al, (1988), Induction of Immune Tolerance During Administration of Monoclonal Antibody to L3 T4 Does not Depend on L3 T4.sup.+ Cells, Underlying Journal of Immunology, 140:713-716; Carteron et al, (1990), F(ab')2 Anti-CD4 and Intact Anti-CD4 Monoclonal Antibodies Inhibit the Accumulation of CD4.sup.+ T Cells, CD8.sup.+ T cells and BT T Cells and B cells in the Kidneys of Lupus-Prone NZB/NZW Mice, Clinical Immunology Immunopathology, 56:373-383.) Thus, this antibody may function like a classical receptor antagonist by: i) block interaction of CD4 with its counter receptor MHC II; ii) or i) causing modulation of CD4 from the cell surface. Under these conditions, CD4.sup.+ T cell responses that require the participation of the CD4 receptor would be attenuated or blocked. The fact that the subject CE9.1 antibody apparently exhibits little depleting activity in humans is advantageous because it may improve safety, may obviate the need for frequent monitoring of CD4.sup.+ cell counts, and may also improve efficacy.

Detail Description Paragraph (26):
[0068] In using the subject CE9.1 monoclonal antibody for the treatment of autoimmune disorders, including for example rheumatoid arthritis, this antibody may be administered by itself or in combination with other compounds suitable for treatment of the particular disease condition. For example, the subject antibody may be administered in combination with other proteins, for example monoclonal antibody soluble receptor proteins to TNF-alpha, monoclonal antibodies to IL2 receptor, monoclonal antibodies and receptor fusion proteins which antagonize the CD40/gp39 interaction and CTLA 4-Ig in monoclonal antibodies which antagonize the B7/CD28 interaction. Also, in the case of treatment of rheumatoid arthritis, the subject antibody may be administered in combination with other therapeutics, for example Rapamycin, Leflunomide, Tenidap, RS-61443 (Mycophenolate Mofetil), Surenyl (sodium Hyaluronate), anti-TCR (V.beta.17) peptide vaccine, Anerva X (anti-MHC vaccine), and extracorporeal protein A immunoabsorbants or combinations thereof. Additionally, the subject antibody may be administered in combination with other antibodies produced according to the invention or known in the art which are specific to human CD4. This may result in synergistic effects, for example, if these antibodies bind to different epitopes of the CD4 protein.

Detail Description Paragraph (105):
[0139] The fact that the antibodies of this invention have utility in inducing immunosuppression means that they are useful in the treatment or prevention of resistance to or rejection of transplanted organs or tissues (e.g., kidney, heart, lung, bone marrow, skin, cornea, etc.); the treatment or prevention of autoimmune, inflammatory, proliferative and hyperproliferative diseases, and of cutaneous manifestations of immunologically medicated diseases (e.g., rheumatoid arthritis, lupus erythematosus, systemic lupus erythematosus, Hashimotos thyroiditis, multiple sclerosis, myasthenia gravis, type 1 diabetes, uveitis, nephrotic syndrome, psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitides, seborrheic dermatitis, Lichen planus, Pemplugus, bullous pemphicjus, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythema, cutaneous eosinophilias, Alopecia areata, etc.); the treatment of reversible obstructive airways disease, intestinal inflammations and allergies (e.g., Coeliac disease, proctitis, eosinophilia gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis) and food-related allergies (e.g., migraine, rhinitis and eczema).

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L7: Entry 6 of 22 File: PGPB Oct 3, 2002

DOCUMENT-IDENTIFIER: US 20020142000 A1
TITLE: Anti-CD3 immunotoxins and therapeutic uses therefor

Detail Description Paragraph (167):
[0198] The immunotoxins can be administered in vivo either alone or in combination with other pharmaceutical agents effective in treating acute or chronic transplant rejection including cyclosporin A, cyclosporin G, rapamycin, 40-O-2-hydroxyethyl-substituted rapamycin (RAD), FK-506, mycophenolic acid, mycophenolate mofetil (MMF), cyclophosphamide, azathioprene, brequinar, leflunamide, mizoribine, deoxyspergualines, 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (FTY 720), corticosteroids (e.g., methotrexate, prednisolone, methylprednisolone, dexamethasone), or other immunomodulatory compounds (e.g., CTLA4-Ig); anti-LFA-1 or anti-ICAM antibodies, or other antibodies that prevent co-stimulation of T cells, for example antibodies to leukocyte receptors or their ligands (e.g., antibodies to MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45, CD58, CD152 (CTLA-4), or CD 154 (CD40 ligand).

Detail Description Paragraph (204):
[0235] In additional aspects of the invention, the immunotoxins of the invention may also be administered to a patient in vivo to treat T-cell-mediated autoimmune disease, such as systemic lupus erythematosus (SLE), type I diabetes, rheumatoid arthritis (RA), myasthenia gravis, and multiple sclerosis, by ablating populations of T cells in the patient.

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L7: Entry 7 of 22 File: PGPB Aug 29, 2002

DOCUMENT-IDENTIFIER: US 20020119150 A1
TITLE: Use of a CD40:CD154 binding interruptor to prevent counter-adaptive immune responses, particularly graft rejection

Detail Description Paragraph (7):
[0018] A number of preclinical studies have established that agents capable of interrupting CD40:CD154 binding have promise as immunomodulating agents. In murine systems, antibodies to CD154 block primary and secondary immune responses to exogenous antigens, both in vitro and in vivo. Antibodies to CD154 cause a reduction in germinal centers in mice and monkeys, consistent with data on CD154 immunodeficiency. Administration of three doses of anti-CD154 antibody to lupus-prone mice, aged three months, substantially reduced titers against double-stranded DNA and nucleosomes, delayed the development of severe nephritis, and reduced mortality. Moreover, administration of anti-CD154 antibodies to mice aged five to seven months with severe nephritis was shown to stabilize or even reverse renal disease. Anti-CD154 antibodies given concomitantly with small resting allogeneic lymphocytes permitted unlimited survival of mouse pancreatic islet allografts. In other animal models, interference with CD40:CD154 binding has been demonstrated to reduce symptoms of autoimmune disease (e.g., multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease), graft rejection (cardiac allograft, graft-versus-host disease), and mercuric chloride induced glomerulonephritis, which is mediated by both humoral and cellular mechanisms.

Detail Description Paragraph (46):
[0057] Combination therapies according to this invention for treatment of graft rejection include the use of anti-CD40L antibodies together with agents targeted at B cells, such as anti-CD19, anti-CD28 or anti-CD20 antibody (unconjugated or radiolabeled), IL-14 antagonists, LJP394 (LaJolla Pharmaceuticals receptor blocker), IR-1116 (Takeda small molecule) and anti-Ig idiotype monoclonal antibodies. Alternatively, the combinations may include T cell/B cell targeted agents, such as CTLA4-Ig, cytokine antagonists such as IL-2 antagonists, IL-4 antagonists, IL-6 antagonists, and IL-15 antagonists, receptor antagonists, anti-CD80/CD86 and anti-B7 monoclonal antibodies, TNF antagonists, LFA1/ICAM antagonists, VLA4/VCAM antagonists, LT/LT.beta., CD2/LFA3 antagonists, brequinar and IL-2 toxin conjugates (e.g., DAB), prednisone, anti-CD3 mAb such as OKT3, mycophenolate mofetil (MMF), cyclophosphamide, CD45RB antagonists, rapamycin, and other immunosuppressants such as calcineurin signal blockers, including without limitation, tacrolimus (FK506). Combinations may also include T cell targeted agents, such as CD4 antagonists, CD2 antagonists and IL-12.

L7: Entry 9 of 22 File: PGPB Aug 15, 2002

DOCUMENT-IDENTIFIER: US 20020110558 A1
TITLE: Use of CD25 binding molecules in the treatment of rheumatoid arthritis or skin diseases

Summary of Invention Paragraph (5):
[0005] Inflammatory and hyperproliferative skin diseases include psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and acne.

Summary of Invention Paragraph (45):
[0045] The CD25 binding molecule may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens or other anti-inflammatory agents. For example, the CD25 binding molecule may be used in accordance with the invention in combination with cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, rapamycin etc.; corticosteroids e.g. prednisone; cyclophosphamide; azathioprene; methotrexate; gold salts, sulfasalazine, antimalarials, brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; other immuno-suppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD28, B7, CD40, CD45, or CD58 or their ligands; or other immunomodulatory compounds, e.g. CTLA4lg.

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L7: Entry 10 of 22 File: PGPB Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020102651 A1
TITLE: Novel B7-4 molecules and uses therefor

Detail Description Paragraph (159):
[0196] In one embodiment, fusion proteins comprising a B7-4 first peptide fused to a second peptide having an activity of another B lymphocyte antigen (e.g., B7-1 or B7-2) can be used to modify T cell mediated immune responses. Alternatively, two separate peptides having an activity of B lymphocyte antigens, (for example, a B7-4 polypeptide with B7-2 and/or B7-1), or a combination of blocking antibodies (e.g., antibodies against a B7-4 polypeptide with anti-B7-2 and/or anti-B7-1 monoclonal antibodies) can be combined as a single composition or administered separately (simultaneously or sequentially), to upregulate or downregulate T cell mediated immune responses in a subject. Furthermore, a therapeutically active amount of one or more peptides having a B7-4 polypeptide activity, with B7-1 and/or B7-1 activity can be used in conjunction with other immunomodulating reagents to influence immune responses. Examples of other immunomodulating reagents include blocking antibodies, (e.g., against CD28, CTLA4, and/or ICOS, or against other T cell markers, or against cytokines), fusion proteins (e.g., CTLA4Ig), or immunosuppressive drugs, (e.g., rapamycin, cyclosporine A or FK506).

Detail Description Paragraph (164):
[0201] Blocking a B7-4 polypeptide function, e.g., by use of a peptide having a B7-4 polypeptide activity alone or in combination with a peptide having B7-1 activity and/or a peptide having B7-2 activity, may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

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L7: Entry 11 of 22 File: PGPB Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020102232 A1
TITLE: Compositions and methods for induction of active autoimmunity

Detail Description Paragraph (145):
[0204] Downmodulation of an immune response is useful, e.g., in situations of tissue, skin and organ transplantation, in graft-versus-host disease (GVHD), allergy, or in autoimmune diseases (such as systemic lupus erythematosus, and multiple sclerosis). In the case of GVHD, the autologous polypeptide preferably a T cell marker and is autologous with respect to the donor of the T cells.

Detail Description Paragraph (148):
[0207] Exemplary disorders that the instant methods can be used to treat include: inhibition of transplantation of organs or tissue, graft-versus-host diseases; rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes uveitis, juvenile-onset or recent-onset diabetes mellitus, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopical dermatitis, contact dermatitis, eczematous dermatitises, seborrhoeis dermatitis, urticaria, Lupus erythematosus, acne, Alopecia areata, keratoconjunctivitis, vernal conjunctivitis, pollen allergies, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, and necrotizing enterocolitis.

Detail Description Paragraph (150):
[0209] To achieve optimal downmodulation of an unwanted immune response in a subject, it may be desirable to additionally administer other agents to the subject. For example, agents that block costimulatory function, e.g., soluble forms of B7-1, B7-2, or B7-1 and B7-2 or blocking antibodies against these antigens prior to or at the time of transplantation. Other downmodulatory agents that can be used include, for example, soluble forms of CTLA4, blocking antibodies against other immune cell markers or soluble forms of other receptor ligand pairs (e.g., agents that disrupt the interaction between CD40 and CD40 ligand (e.g., anti CD40 ligand antibodies)), antibodies against cytokines, fusion proteins (e.g., CTLA4-Fc), and immunosuppressive drugs, (e.g., rapamycin, cyclosporine A or FK506).

Detail Description Table CWU (1):
1 Target autologous Disease antigen Reference(s) Sickle cell disease CD64, sL-selectin, Lard, L. R. et al., J. (SCD) elastase, sCD16 Leukoc. Biol. 66:411-5 (1999) Systemic lupus CD46 Kawano, M. et al., Clin. erythematosus (SLE) Exp. Immunol. 116:542-6 (1999) CNS demyelinating TNF-.alpha. Kahn, M. A. et al., J. diseases Neuroimmunol. 95:19-34 (1999) Inflammatory bowel sL-selectin Seidelin, J. B. et al., Am. J. disease (IBD) Gastroenterol. 93:1854-9 (1998) Inflammatory bowel TNF-.alpha. Hanauer, S. B. et al., disease (IBD) Aliment Pharmacol. Ther. 13:16-22 (1999) Renal cell carcinoma sTNF-R75 Elsasser-B., U. et al., (RCC) Anticancer Res. 18:1883-90 (1998) Alcoholic liver sTNF-R55 aveau, S. et al., J. Hepatol. cirrhosis 28:778-84 1998) Acute alcoholic sTNF-R75 Naveau, S. et al., J. hepatitis Hepatol. 28:778-84 (1998) Rheumatoid arthritis TNF-.alpha. Alexopoulou, L. et al., Eur. J. Immunol. 27:2588-92 (1997) Hanauer, S. B. et al., Aliment Pharmacol. Ther. 13:16-22 (1999) Metastasis of TGF-.beta. Moretti, S. et al., melanoma Melanoma Res. 7:313-21 (1997) Carotid CD40, Mach, F. et al., Nature atherosclerosis CD40L (CD154) 394:200-3 (1998) Carotid Lipoprotein (a) Yamamoto, M. et al., atherosclerosis Diabetes Care

20:829-31 (1997) Chronic myeloid CD56 Lanza, F. et al., Leukemia leukemia (CML) 7:1570-5 (1993) Rejection of heart IL-10, Furukawa, Y. et al., Am. J. transplantation IFN-.gamma. Pathol. 155:1929-39 (1999) Rejection of kidney IL-2, IL-2R Gelder, T. et al., transplantation Transplantation 60:248-52 (1995) Advanced acute CD45 Matthews, D. C. et al., leukemia Blood 94:1237-47 (1999) Allergy and IL-4, Barnes, P. J. et al., N. Engl. chronic asthma IgE J. Med. 341:2006-8 (1999) Milgrom, H. et al., N. Engl. J. Med. 341:1966-73 (1999) Chang, T. W. et al., Biotechnol. 8:122-6 (1990) Breast cancer EGFR, TGF-.beta. Ma, L. et al., Int. J. Cancer 78:112-9 (1998) Intestinal CD54 (ICAM-1) Krieglstein, C. F. et al., Int. inflammation J. Colorectal Dis. 14:219-23 (1999) Schneider, D. et al., Eur. Neurol. 40:78-83 Lupus nephritis CD40L (CD154) Kalled, S. L. et al., J. Immunol. 160:2158-65 (1998) Metastasis of breast sCD44 v5 Lackner, C. et al., Breast cancer Cancer Res. Treat. 47:29-40 (1998) Adult T-cell Fas-R (CD95) Kamihira, S. et al., Br. J. Leukemia (ATL) Haematol. 99:858-65 (1997)

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L7: Entry 19 of 22 File: USPT Oct 24, 2000

DOCUMENT-IDENTIFIER: US 6136310 A
TITLE: Recombinant anti-CD4 antibodies for human therapy

Brief Summary Text (5):
Apart from RA, CD4.sup.+ cells have also been implicated in other chronic conditions including psoriasis, insulin-dependent diabetes mellitus, systemic lupus erythematosus and inflammatory bowel diseases. Moreover, it is probable that CD4 expression may be involved in other autoimmune diseases.

Brief Summary Text (8):
Essentially, the objective of anti-CD4 mAb therapy is to arrest the autodestructive activity of CD4.sup.+ cells, particularly during acute phases of autoimmune disorder. The ultimate therapeutic goal is to impose a state of immunological unresponsiveness (anergy) or long-term tolerance to the insulting antigens (or specific tissues) that sustain the underlying disease, without compromising normal host defenses against opportunistic infections. Apart from RA, CD4 mAbs may also be beneficial for the treatment of other autoimmune diseases, e.g., insulin-dependent diabetes mellitus, systemic lupus erythomatosis, psoriasis, inflammatory bowel disease, and multiple sclerosis.

Detailed Description Text (14):
Therefore, the present invention provides specific recombinant antibodies which are primate/human chimeric monoclonal antibodies which are directed against the human CD4 antigen which exhibit improved properties, e.g., low T cell depleting activity and greater stability. Given these properties, these recombinant antibodies have particular utility as immuno-modulators and are especially useful for the treatment of autoimmune diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus (SLE) as well as non-auto immune indications such as graft-versus-host disease (GVHD) transplant rejection, asthma and HIV. Also, the subject antibodies possess utility as adjuncts in genetic therapy. In particular, the subject antibodies may be administered prior to, concurrent or after administration of a vector (containing a therapeutic DNA) to prevent or reduce the host humoral response to said vector. These diseases are exemplary of CD4 related conditions.

Detailed Description Text (18):
Potent immunomodulatory activity has been observed with the CE9.1 antibody both in vitro and in vivo. Given these properties, i.e., reduced immunogenicity, slower serum clearance and potent immuno-modulation, in comparison to other known anti-human CD4 mAbs that are murine or rodent derived, this antibody as well as the other antibodies described herein should be particularly suitable for long term therapy of diseases where immunosuppression is desirable, e.g., autoimmune disorders and chronic inflammatory diseases such as rheumatoid arthritis. However, it is expected that these antibodies should be useful for the treatment of many other disease conditions including, by way of example, Hashimoto's thyroiditis, primary myxoedema, thyrotoxicosis/Graves disease, pernicious anaemia, autoimmune atrophic gastritis, autoimmune carditis, Addison's disease, premature menopause, type I-diabetes mellitus, Good pasture's syndrome, myasthenia gravis, multiple sclerosis, male infertility, pemphigus vulgaris, pemphigoid, sympathetic ophthalmia, phacogenic uveitis, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, idiopathic leucopenia, primary biliary cirrhosis, active chronic hepatitis (HBs Ag negative), cryptogenic cirrhosis, inflammatory bowel disease syndrome, Sjogren's syndrome, psoriasis, rheumatoid arthritis, dermatomyositis, scleroderma, mixed tissue connective disease, discoid lupus erythematosus, systemic vasculitis, and

systemic lupus erythematosus (SLE).

Detailed Description Text (20):
Essentially, the exemplified recombinant anti-CD4 monoclonal antibodies described in this application or other antibodies produced according to the present invention and as described in the above-referenced application (incorporated by reference) will likely mediate therapeutic activity by arresting or altering the destructive activity of CD4.sup.+ cells, particularly during acute phases of autoimmune disorders such as rheumatoid arthritis. Thus, administration of antibodies according to the invention will result in a state of immunological unresponsiveness (anergy) or long term tolerance to the insulting antigens (or specific tissues) that sustain the underlying disease without compromising normal host defenses against opportunistic infections. Apart from RA, CD4 monoclonal antibodies should be beneficial in the treatment of the above-identified diseases and afford particular application for the treatment of insulin-dependent diabetes mellitus, systemic lupus erythematosus, cirrhosis, inflammatory bowel disease, multiple sclerosis, as well as other auto-immune diseases. They may also be useful in the treatment of non-autoimmune diseases such as leukemia lymphoma graft-versus-host disease, transplant rejection, asthma and HIV.

Detailed Description Text (32):
The CE9.1 antibody has also been tested in humans. For example, the activity of the CE9.1 antibody has also been evaluated in single dose-escalating phase 1 trials in rheumatoid arthritis patients. These results were very promising. Specifically, about half of the patients who were administered exhibited at least a 30% improvement in their tender joint scores, with the adverse event profile being extremely benign. Moreover, as discussed supra, while it was initially assumed that CE9.1 would be depleting, in fact this antibody exhibited only partial and transient depletion upon single administration. The partial non-depleting nature of this antibody may be beneficial because in a number of animal studies it has been reported that CD4.sup.+ T cell depletion is apparently not necessary for efficacy of CD4 monoclonal antibodies. (See Carteron et al., Induction of Immune Tolerance During Administration of Monoclonal Antibody to L3 T4 Does not Depend on L3 T4.sup.+ Cells, Underlying Journal of Immunology, 140:713-716 (1988); Carteron et al, F(ab')2 Anti-CD4 and Intact Anti-CD4 Monoclonal Antibodies Inhibit the Accumulation of CD4.sup.+ T Cells, CD8.sup.+ T cells and BT T Cells and P cells in the Kidneys of Lupus-Prone NZB/NZW Mice, Clinical Immunology Immunopathology, 56:373-383 (1990).) Thus, this antibody may function like a classical receptor antagonist by: i) blocking interaction of CD4 with its counter receptor MHC II; or ii) causing modulation of CD4 from the cell surface. Under these conditions, CD4.sup.+ T cell responses that require the participation of the CD4 receptor would be attenuated or blocked. The fact that the subject CE9.1 antibody apparently exhibits little depleting activity in humans is advantageous because it may improve safety, may obviate the need for frequent monitoring of CD4.sup.+ cell counts, and may also improve efficacy.

Detailed Description Text (54):
In using the exemplified chimeric anti-CD4 antibodies or other chimeric antibodies produced according to the invention as immunosuppressants or CD4 modulators for the treatment of autoimmune disorders, including for example rheumatoid arthritis, such antibodies may be administered alone or in combination with other compounds suitable for treatment of the particular disease condition. For example, the subject antibody may be administered in combination with other proteins, for example monoclonal antibody soluble receptor proteins to TNF-alpha, monoclonal antibodies to IL2 receptor, monoclonal antibodies and receptor fusion proteins which antagonize the CD40/gp39 interaction and CTLA 4-Ig in monoclonal antibodies which antagonize the B7/CD28 interaction. Also, in the case of treatment of rheumatoid arthritis, the subject antibody may be administered in combination with other therapeutics, for example Rapamycin, Leflunomide, Tenidap, RS-61443 (Mycophenolate Mofetil), Surenyl (sodium Hyaluronate), anti-TCP (V.beta.17) peptide vaccine, Anerva X (anti-MHC vaccine), and extracorporeal protein A immunoabsorbents or combinations thereof. Additionally, the subject antibody may be administered in combination with other antibodies produced according to the invention or known in the art which are specific to human CD4. This may result in synergistic effects, for example, if these antibodies bind to different epitopes of the CD4 protein.

Detailed Description Text (213):
The fact that the antibodies of this invention have utility in inducing immunosuppression means that they are useful in the treatment or prevention of resistance to or rejection of transplanted organs or tissues (e.g., kidney, heart, lung, bone marrow, skin, cornea, etc.); the treatment or prevention of autoimmune, inflammatory, proliferative and hyperproliferative diseases, and of cutaneous manifestations of immunologically medicated diseases (e.g., rheumatoid arthritis, lupus erythematosus, systemic lupus erythematosus, Hashimotos thyroiditis, multiple sclerosis, myasthenia gravis, type 1 diabetes, uveitis, nephrotic syndrome, psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitides, seborrheic dermatitis, Lichen planus, Pemplugus, bullous pemphicjus, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythema, cutaneous eosinophilias, Alopecia areata, etc.); the treatment of reversible obstructive airways disease, intestinal inflammations and allergies (e.g., Coeliac disease, proctitis, eosinophilia gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis) and food-related allergies (e.g., migraine, rhinitis and eczema). Also, the subject antibodies have potential utility for treatment of non-autoimmune conditions wherein immunomodulation is desirable, e.g., graft-versus-host disease (GVHD), transplant rejection, asthma, HIV, leukemia, lymphoma, among others.

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L7: Entry 22 of 22 File: USPT May 5, 1998

DOCUMENT-IDENTIFIER: US 5747034 A
TITLE: Methods and materials for the induction of T cell anergy

Detailed Description Text (73):
The anti B7-1 antibodies of the invention (or other molecules that bind to the B7-1 antigen) are given in combination with one or more immunosuppressive agents. Immunosuppressive agents are agents that block or inhibit the activation or proliferation of T cells. The immunosuppressive agents according to this invention include cyclosporin A (CsA), corticosteroids (methotrexate, prednisolone, dexamethasone), FK506, and rapamycin. Preferably the immunosuppressive agent is cyclosporin A, FK506 or a corticosteroid, most preferably cyclosporin A.

Detailed Description Text (75):
The antibodies and compositions of this invention are administered at a concentration that is therapeutically effective to halt transplant rejection, or prevent or treat (1) GVHD or rheumatoid arthritis, or (2) antibody-mediated diseases such as allergies, SLE, PBC and ITP. To accomplish this goal, the antibodies or compositions may be formulated using a variety of acceptable excipients known in the art. Typically, the antibodies or compositions are administered by injection, either intravenously or intraperitoneally. Methods to accomplish this administration are known to those of ordinary skill in the art. It may also be possible to obtain compositions which may be topically or orally administered, or which may be capable of transmission across mucous membranes.

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L8	('b7-1') same ('b7-2')same (antibod$) and (sle or lupus)	119	L8
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L7	L6 and (sle or lupus)	22	L7
L6	b7$ same (antibod$) same (rapamycin)	35	L6
L5	L4 and (sle or lupus)	125	L5
L4	b7$ and rapamycin	185	L4
L3	L2 and b7$	1	L3
L2	collins-mark$	80	L2
L1	sypek-joseph$	1	L1

END OF SEARCH HISTORY

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L8: Entry 11 of 119 File: PGPB Nov 28, 2002

DOCUMENT-IDENTIFIER: US 20020176855 A1
TITLE: HUMANIZED IMMUNOGLOBULIN REACTIVE WITH B7-2 AND METHODS OF TREATMENT THEREWITH

Summary of Invention Paragraph (13):
[0011] Additional methods encompassed by the invention include a method of inhibiting the interaction of a first cell bearing a B7-2 receptor with a second cell bearing B7-2, comprising contacting the second cell with an effective amount of a humanized immunoglobulin, as described herein. Accordingly, the invention relates to various methods of treatment. The invention includes a method for modulating an immune response of a patient or treating a patient having a transplanted organ, tissue, cell or the like comprising administering an effective amount of the humanized immunoglobulin, as described herein, in a carrier (e.g., pharmaceutical carrier), wherein the immune response is modulated. The invention pertains to treating acute and/or chronic transplant rejection for a prolonged periods of time (e.g., days, months, years). The invention also pertain to methods of treating a disease associated with modulation of the B7-2 molecule (e.g., autoimmune diseases, infectious diseases, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis), comprising administering to a patient an effective amount (e.g., a therapeutically effective amount) of a humanized immunoglobulin, as described herein, in a carrier. Accordingly, the invention encompasses a pharmaceutical composition comprising the humanized antibody, as described herein.

Summary of Invention Paragraph (16):
[0014] The invention relates to methods for treating a patient having a disease comprising administering a therapeutically effective amount of a humanized immunoglobulin specific to B7-1 and a therapeutically effective amount of a humanized immunoglobulin specific to B7-2. The diseases, as described herein, include, for example, autoimmune diseases, infectious diseases, asthma, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis. This method also pertains to modulating the immune response of a patient having a transplanted organ, tissue, cell or the like comprising administering an effective amount of a humanized immunoglobulin that binds to B7-1 and a humanized immunoglobulin that binds to B7-2. Such diseases are described herein.

Detail Description Paragraph (58):
[0087] The B7:CD28/CTLA-4 pathway participates in various disease states including the pathogenesis of infectious diseases, asthma, autoimmune diseases, inflammatory disorders, the rejection of grafted organs and graft versus host disease. This pathway also participates in prophylaxis and mechanisms that stimulate the immune system. Transfection with genes encoding costimulators, such as B7, are applicable for anti-tumor tumor and anti-viral vaccines. Also, the B7 molecules participate in autoimmune diseases such as systemic lupus erythematosus, diabetes mellitus, insulitis, arthritis, inflammatory bowel disease, inflammatory dermatitis (psoriasis vulgaris and atopic dermatitis), and multiple sclerosis. Reiser, Hans, M. D., et al., Mechanisms of Disease, New England J. of Med., Vol 335, No. 18, 1369 (1996).

Detail Description Paragraph (60):
[0089] Therefore, modulating or influencing the B7-2's role can be useful in treating patients with these diseases. B7-2 modulation is also useful in treating patients with immune-related or autoimmune diseases and disorders in which B7-2

participates. The modulation of B7-2 can also be used for diseases related to or affected by IL-4 and/or the generation of type 2 helper cells. These disorders/diseases can be treated using an antibody specific to B7-2. Preferably, the antibody is a humanized antibody specific to B7-2. Treatment of these diseases may be facilitated with co-administration of an anti-B7-2 antibody, including chimeric and humanized versions thereof, with an anti-B7-1 antibody, or antibodies to the corresponding receptors, CD28 and CTLA-4. Methods of treatment also involve co-administration of a humanized anti B7-2 antibody or humanized anti B7-1 antibody with other standard therapy drugs, such methotrexate, cyclosporin, steroids, .alpha. CD40 ligands.

Detail Description Paragraph (61):
[0090] The invention includes methods for transplanting cells (e.g., blood cells or components, or bone marrow) to a patient in need thereof. A patient in need thereof is one, for example, having a disease that is treated with such a transplant (e.g., proliferative diseases such as leukemia, lymphoma, cancer), anemia such as sickle-cell anemia, thalassemia, and aplastic anemia) and myeloid dysplasia syndrome). The method comprises obtaining cells from a donor. Generally, donor bone marrow contains both immature and mature lymphocytes. The blood cells from a donor can be stem cells or immature blood cells in addition to bone marrow cells. The cells of the donor preferably comes from a person who has similar characteristics as the patient/recipient (e.g., the donor's bone marrow is a match to the patient's bone marrow). The characteristics that are analyzed to determine whether a donor is a match to the patient are MHC class 1 and 2 (e.g., HLA-A, HLA-B, and/or HLA-DR). The method involves contacting the cells (e.g., bone marrow or other blood components) with an immunoglobulin specific to B7-1 and/or an immunoglobulin specific to B7-2 and recipient cells (e.g., lymphocyte from the patient) to obtain a mixture (e.g., treated cells). The donor cells, immunoglobulin(s) and recipient cells are in contact for a period of time sufficient for tolerance induction (e.g., about 1-48 hours, preferably about 36 hours). Tolerance induction (e.g., anergy) refers to the lack of responsiveness to an antigen that has been induced with a treatment with B7-1 and/or B7-2 antibodies, such that the T-cell can no longer adequately or fully respond to that antigen. Example 9. The recipient cells (e.g., Peripheral Blood Lymphocytes (PBL), or lymphocytes that express class I antigens (MHC-I)) are radiated to prevent cells from dividing. A substitute for recipient cells can be tissue, organs or engineered cells that express MCH class I antigens, and B7-1 and/or B7-2 molecules. The method then includes introducing the mixture (e.g., treated cells) or bone marrow to the patient. This method of treatment is aimed at preventing graft vs. host disease. For example, cells in the treated bone marrow become tolerant to recipient alloantigen thereby reducing or eliminating graft vs. host disease. Accordingly, the claimed methods include treatment, preventing or aiding in the prevention of graft vs. host disease. The anti B7-1 and B7-2 antibodies reduce rejection of the donor bone marrow. However, the methods are able to reduce rejection without significantly compromising the patient's ability to detect and develop an immune response to other foreign cells and antigens. Hence, the methods allows the transplantation to be recipient specific and reject foreign antigens without compromising the transplant. See Exemplification Section.

Detail Description Paragraph (103):
[0122] Binding assays were begun by plating cells onto 96-well tissue culture plates at 10,000 CHO/hB7-2 cells per well. Two days later, adherent cells were gently washed with assay buffer containing nonfat dry milk protein (for blocking nonspecific binding) and sodium azide (to prevent internalization of antibodies by cells). For direct binding assays, .sup.125I-labeled anti-B7 antibodies (I.sup.125-murine anti-human B7-2; 826 cpm/fmol; humanized anti-human B7-2, 883 cpm/fmol) were serially diluted in assay buffer and incubated on cells overnight, allowing antibodies to bind to cell-surface B7 and come to equilibrium. Unbound antibody was gently washed from cells, and bound .sup.125I labeled antibody was detected using an .sup.125I scintillant and photodetector system. Non-specific binding to CHO cells was determined for each dilution in the same manner, but on cells expressing the B7-1 molecule that is not recognized by the antibody being tested.

Detail Description Paragraph (129):
[0142] In the primary MCR, the additional anti-B7-1 mAb alone had no inhibitory

effect indicating a minor role for B7-1 alone in driving proliferation of responder T cells. Anti-B7-2 alone inhibited T cell proliferation on all days tested at a level comparable to hCTL4Ig, a recombinant protein known to bind to both B7-1 and B7-2. The combination of anti-B7-1 and anti-B7-2 was the most effective inhibitor of T cell proliferation that completely inhibited this response on all days tested. The superior ability of the combined anti-B7-1 and anti-B7-2 to inhibit T cell proliferation, as compared to hCTL4Ig, reflects the higher affinity of the anti-B7 mAbs for B7-1 and B7-2 as compared to hCTL4Ig. The combined anti-B7-1 and anti-B7-2 mAbs were better inhibitors of T cell proliferation than anti-B7-2 alone, demonstrating the need to block both stimulatory receptors to completely inhibit T cell responses. These results show that complete blockade of the B7-1 and B7-2 costimulators more completely abrogates alloresponsiveness in the MLR. Accordingly, these results indicate that methods of treatment including both anti B7-1 and anti B7-2 antibodies will be even more effective than either of the antibodies alone, especially where both costimulatory molecules are functional. While the responder/stimulator pair, described herein, was not sensitive to inhibition by anti-B7-1 alone, some responder/stimulator pairs do exhibit moderate (0-50%) anti-B7-1 sensitivity.

Detail Description Paragraph (156):
[0163] NODscid mice were populated with human lymphocytes by the administration of 10e8 human PBLs. After 28 days, the mice were treated with TSST-1 (10 mg, I.P.) with or without the treatment with the combined antibodies to human B7-1 and B7-2 (500 mg, I.V.). After 14 additional days, the presence of human lymphocytes, T-cells, and TSST-1 specific T-cells (VP2-TCR-cells) in the peritoneal cavity was measured by FACS using antibodies specific for human CD45, CD4, and human V.beta.2-TCR.

CLAIMS:

47. A method of treating a patient with a disease selected from the group consisting of: autoimmune diseases, infectious diseases, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis, comprising administering a therapeutically effective amount of a humanized immunoglobulin specific to B7-2 to the patient.

52. A method for treating a patient with a disease selected from the group consisting of: autoimmune diseases, infectious diseases, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, asthma, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis, comprising administering a therapeutically effective amounts of a humanized immunoglobulin specific to B7-1 and a therapeutically effective amount of a humanized immunoglobulin specific to B7-2.

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L8: Entry 70 of 119 File: USPT Aug 6, 2002

DOCUMENT-IDENTIFIER: US 6429303 B1
TITLE: Nucleic acids encoding members of the human B lymphocyte activation antigen B7 family and methods of using the same

Detailed Description Text (242):
Autoimmune disorders which may be treated using a polypeptide of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a polypeptide of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a polypeptide of the present invention.

Detailed Description Text (244):
Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to energize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of B lymphocyte antigens.

Detailed Description Text (246):
Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and auto-antibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of auto-antibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of

well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., FUNDAMENTAL IMMUNOLOGY, Raven Press, New York, 1989, pp. 840-856).

L8: Entry 88 of 119 File: USPT Jul 18, 2000

DOCUMENT-IDENTIFIER: US 6090914 A
TITLE: CTLA4/CD28Ig hybrid fusion proteins and uses thereof

Brief Summary Text (23):
There is a need for molecules which can identify in vitro B7 positive B cells, i.e., activated B cells, for leukocyte typing and FAC sorting. Further, there is a need for molecules which may be used to prevent the rejection of organ transplants and inhibit the symptoms associated with lupus erythmatosus and other autoimmune diseases. In the past, major therapies relied on panimmunosuppressive drugs, such as cyclosporine A or monoclonal antibodies (MAbs) to CD3 to prevent organ transplants or inhibit symptoms of lupus. Unfortunately, these drugs must frequently be taken for the life of the individual, depress the entire immune system, and often produce secondary health ailments such as increased frequency of infections and cancer.

Brief Summary Text (25):
Accordingly, the present invention provides the complete and correct DNA sequence encoding the amino acid sequence corresponding to the CTLA4 receptor protein, and identifies B7 antigen (e.g. B7-1 and B7-2 antigens) as a natural ligand for the CTLA4 receptor. The invention also provides a method for expressing the DNA as a CTLA4 immunoglobulin (Ig) fusion protein product. Embodiments of the invention include CTLA4Ig fusion protein, and hybrid fusion proteins including CD28/CTLA4Ig fusion proteins (which is also referred to herein as the CTLA4/CD28Ig fusion protein). Also provided are methods for using the CTLA4 fusion protein, B7Ig fusion protein, hybrid fusion proteins, and fragments and/or derivatives thereof, such as monoclonal antibodies reactive with CTLA4 and the B7 antigen, to regulate cellular interactions and immune responses.

L8: Entry 114 of 119 File: USPT May 5, 1998

DOCUMENT-IDENTIFIER: US 5747034 A
TITLE: Methods and materials for the induction of T cell anergy

Detailed Description Text (4):
Monoclonal antibody B7-24 is an unique monoclonal antibody that binds specifically to the B7-1 molecule, but not to B7-2. This is in contrast with a recombinant fusion protein of the CTLA-4 molecule (Linsley, J. Exp. Med., 174, 561 (1991), which binds to both B7-1 and B7-2. Monoclonal antibody B7-24 is also different from the anti-B7 monoclonal antibody BB-1, which binds to B7-1 and in addition to a third form of the B7 molecule, B7-3 (Boussiotis et al., Proc. Nat'l. Acad. Sci. (USA), 90, 11059 (1993)). Although it is known that both B7-1 and B7-2 can co-stimulate T cells by binding to the CD28 molecule, it is not known that blocking only B7-1 with a specific monoclonal antibody such as B7-24, when combined with an immunosuppressive drug such as cyclosporin A, can induce T-cell tolerance or anergy. This is unexpected since it has been suggested in the literature that CsA can prevent anergy induction in mice [Schwartz, Science, 248, 425 (1990)].

Detailed Description Text (75):
The antibodies and compositions of this invention are administered at a concentration that is therapeutically effective to halt transplant rejection, or prevent or treat (1) GVHD or rheumatoid arthritis, or (2) antibody-mediated diseases such as allergies, SLE, PBC and ITP. To accomplish this goal, the antibodies or compositions may be formulated using a variety of acceptable excipients known in the art. Typically, the antibodies or compositions are administered by injection, either intravenously or intraperitoneally. Methods to accomplish this administration are known to those of ordinary skill in the art. It may also be possible to obtain compositions which may be topically or orally administered, or which may be capable of transmission across mucous membranes.

Detailed Description Text (180):
Monoclonal antibody B7-24 binds to a different antigenic epitope on the B7-1 molecule than the BB-1 monoclonal antibody and the CTLA-4 Ig fusion protein: B7-24 does not bind to B7-2, whereas CTLA-4 Ig does; B7-24 and CTLA-4 Ig do not bind to B7-1 negative cells, which are positive for staining with BB-1 monoclonal antibody. [Boussiotis et al., Proc. Nat'l. Acad. Sci. (USA), 90, 11059 (1993); and Freeman et al., Science, 262, 909 (1993)].

Detailed Description Text (183):
Induction of tolerance in an in vivo model of heart transplantation in rats with CTLA-4 Ig is reported only to work when added 2 days after the tissue grafting. Starting the treatment at the same day of the grafting is not reported to result in tolerance. Thus, signaling by B7-2 interaction with T cells is needed for tolerance induction and the blocking effect at day 2 is due to blocking B7-1. With the B7-24 antibody, this is not a problem because in contrast to CTLA-4 Ig, it does not block B7-2. With respect to tolerance induction versus suppression combination of anti-B7-1 with CsA is not obvious signal transduction through the TcR/CD3 complex and anti-B7-2 are needed for tolerance induction. This means that the signals by the TcR/CD3 and B7-2 needed for IL-2 production are sensitive for CsA, but the signal for tolerance induction is not.

Detailed Description Paragraph Table (7):
TABLE 7

Antibody	B7-1	B7-2	B7-3
B7-24	+	-	-
BB-1	+	-	+
CTLA-4Ig	+	+	-

CLAIMS:

1. A method for treating transplant rejection in a patient, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of (a) an antibody or an antigen binding fragment thereof that binds to the B7-1 antigen but not to the B7-2 and B7-3 antigens; and (b) an immunosuppressive agent in a pharmaceutically acceptable excipient.

2. A method for treating graft versus host diseases (GVHD) in a patient, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of (a) an antibody or an antigen binding fragment thereof that binds to the B7-1 antigen but not to the B7-2 and B7-3 antigens; and (b) an immunosuppressive agent in a pharmaceutically acceptable excipient.

3. A method for treating rheumatoid arthritis in a patient, the method comprising administering to a patient in need of such treatment a therapeutically effective amount of (a) an antibody or an antigen binding fragment thereof that binds to the B7-1 antigen but not to the B7-2 and B7-3 antigens; and (b) an immunosuppressive agent in a pharmaceutically acceptable excipient.

12. A composition for inducing T cell anergy comprising in combination:

a) a monoclonal antibody or an antigen binding fragment thereof, said antibody or fragment capable of specifically binding to the B7-1 antigen but not to the B7-2 and B7-3 antigens on the surface of an antigen presenting cell, and

b) an immunosuppressive agent; said antibody or fragment and said immunosuppressive agent each being present in an amount that is effective to induce a T cell anergy by the combination that is greater than the sum of the T cell anergies induced by the same amount of each of the components alone.

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L8: Entry 119 of 119 File: DWPI Nov 28, 2002

DERWENT-ACC-NO: 2000-524532
DERWENT-WEEK: 200281

TITLE: Humanized immunoglobulin having a binding specificity to B7-1 (derived from ATCC PTA-263), or B7-2 (derived from ATCC CRL-12524) molecules, modulates immune responses and can therefore treat e.g. autoimmune diseases, infectious diseases

PRIORITY-DATA: 1999US-0339596 (June 24, 1999), 1999US-0249011 (February 12, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20020176855 A1	November 28, 2002		000	C07H021/02
WO 200047625 A2	August 17, 2000	E	158	C07K016/28
AU 200039988 A	August 29, 2000		000	C07K016/28
NO 200103911 A	October 10, 2001		000	C07K000/00
EP 1159300 A2	December 5, 2001	E	000	C07K016/28
CZ 200102925 A3	January 16, 2002		000	C07K016/28
BR 200008209 A	February 19, 2002		000	C07K016/28
KR 2002002389 A	January 9, 2002		000	C07K016/28
CN 1360596 A	July 24, 2002		000	C07K016/28

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US20020176855A1	February 12, 1999	1999US-0249011	
WO 200047625A2	February 9, 2000	2000WO-US03303	
AU 200039988A	February 9, 2000	2000AU-0039988	
AU 200039988A		WO 200047625	Based on
NO 200103911A	February 9, 2000	2000WO-US03303	
NO 200103911A	August 10, 2001	2001NO-0003911	
EP 1159300A2	February 9, 2000	2000EP-0919275	
EP 1159300A2	February 9, 2000	2000WO-US03303	
EP 1159300A2		WO 200047625	Based on
CZ 200102925A3	February 9, 2000	2000WO-US03303	
CZ 200102925A3	February 9, 2000	2001CZ-0002925	
CZ 200102925A3		WO 200047625	Based on
BR 200008209A	February 9, 2000	2000BR-0008209	
BR 200008209A	February 9, 2000	2000WO-US03303	
BR 200008209A		WO 200047625	Based on
KR2002002389A	February 9, 2000	2000WO-US03303	
KR2002002389A	August 13, 2001	2001KR-0710260	
KR2002002389A		WO 200047625	Based on
CN 1360596A	February 9, 2000	2000CN-0806200	

INT-CL (IPC): A61 K 31/445; A61 K 31/56; A61 K 35/12; A61 K 38/13; A61 K 39/395; A61 K 39/40; A61 K 39/42; A61 K 39/505 ; A61 P 1/00; A61 P 1/18; A61 P 3/00; A61 P 7/06; A61 P 17/00; A61 P 19/02; A61 P 25/00; A61 P 35/00; A61 P 37/00; C07 H 21/02; C07 H 21/04; C07 K 0/00; C07 K 16/00; C07 K 16/28; C12 N 1/20; C12 N 5/00; C12 N 5/06; C12 N 5/10; C12 N 5/12; C12 N 5/16; C12 N 15/00; C12 N 15/09; C12 N 15/13; C12 N 15/62; C12 N 15/63; C12 N 15/70; C12 N 15/74; C12 N 15/85; C12 N 15/87; C12 P 21/04; C12 P 21/08; G01 N 33/577; G01 N 33/68; A61 K 39:00; A61 K 39/395; A61 K 39/395; A61 K 39/395; A61 K 39/395; A61 K 38:13; A61 K 31:56 ; A61 K 31:445

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L8: Entry 119 of 119 File: DWPI Nov 28, 2002

DERWENT-ACC-NO: 2000-524532
DERWENT-WEEK: 200281

TITLE: Humanized immunoglobulin having a binding specificity to B7-1 (derived from ATCC PTA-263), or B7-2 (derived from ATCC CRL-12524) molecules, modulates immune responses and can therefore treat e.g. autoimmune diseases, infectious diseases

Basic Abstract Text (3):
(1) a host cell comprising nucleic acid that encodes a humanized B7-1 antibody and/or a humanized B7-2 antibody;

Basic Abstract Text (14):
(a) determining the complementarity determining regions (CDRs) of an antibody of non-human origin which has binding specificity for B7-1 or B7-2;

Basic Abstract Text (18):
(a) contacting the sample with an antibody specific to B7-1 or B7-2 to allow complex formation; and

Basic Abstract Text (25):
(15) a method for treating a disorder selected from autoimmune diseases, infectious diseases, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, asthma, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis comprising administering a humanized immunoglobulin to B7-1 and B7-2

Basic Abstract Text (27):
(17) a method for decreasing an antibody response to an antigen in a mammal comprising administering a humanized immunoglobulin specific to B7-1 or B7-2.

Basic Abstract Text (31):
USE - The humanized immunoglobulin with binding specificity to B7-1 and/or B7-2 is useful for treating autoimmune diseases, infectious diseases, inflammatory disorders, systemic lupus erythematosus, diabetes mellitus, insulitis, asthma, arthritis, inflammatory bowel disease, inflammatory dermatitis, and multiple sclerosis. The immunoglobulins are also useful for treating a transplant recipient or preventing transplant rejection in a transplant recipient, and treating proliferative disease (leukemia, lymphoma and cancer), anemia (sickle-cell anemia, thalassemia and aplastic anemia), inborn errors of metabolism, congenital immunodeficiency diseases, and myeloid dysplasia syndrome.

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B7-2.DWPI,EPAB,JPAB,USPT,PGPB.	514
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LUPU.DWPI,EPAB,JPAB,USPT,PGPB.	288
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